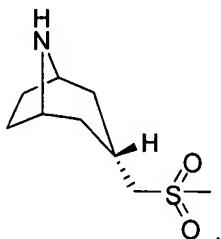


REMARKS

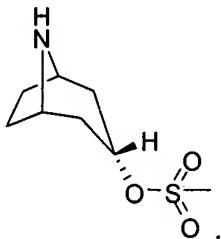
AMENDMENTS

Entry 56 in Table 1 has been amended to include the structure which is recited by the name. In addition, the name of the original structure has been added to entry 56.

Paragraph [0302] has been amended to correct a naming error in one of the intermediates, incorrectly named (3-*endo*)-3-[(methylsulfonyl)methyl]-8-azabicyclo[3.2.1]octane (emphasis added) and depicted below



The name should have been (3-*endo*)-3-[(methylsulfonyl)oxy]-8-azabicyclo[3.2.1]octane (emphasis added) whose structure is depicted below:



An oxygen was inadvertently omitted from the structure when the intermediate was automatically named using naming software. A person of ordinary skill in the art would recognize that the final compound cannot be made with the incorrectly-named intermediate and that the oxygen is necessary to yield the final product recited in the synthetic example. The final product, as named, correctly contains the oxygen. The final product was characterized by mass spectrometry and NMR and the data given in the example is consistent with the final product as named.

In the December 19, 2007 Preliminary Amendment, “lower” in R² of Claim 67 was inadvertently struck through. It has been added back in.

In order to expedite prosecution, the Applicants have amended the Claims to delete “hydrate.” In addition, to expedite examination, the Applicants have deleted

“geometric isomer” from the claims. The Applicants respectfully point out that the term “geometric isomer” is recognized by a person of ordinary skill in the art as a subset of the term “stereoisomer” and thus is encompassed by the claimed term stereoisomer.

Claims are amended to remove nonelected subject matter, to correct punctuation and typographical errors, and to particularly point out and distinctly claim what the Applicants regard as their invention. Support for the above amendments and new claims are found throughout the Specification. The Applicants believe that no new matter is introduced with the above amendments and new claims. The Applicants respectfully request that they be entered into the record.

Request for Reconsideration of Final Restriction Requirement

Applicants have claimed generic scope and specific compounds which do not fall within any of the restriction groups as drafted by the Office. All restrictions groups are directed to Compounds of Formula I only. Compounds in Claims 123 and 124 do not fall within the scope of Formula I but they are intermediates useful in the synthesis of Compounds of Formulas I and Ia. In addition, Applicants have claimed generic scope directed to Compounds of Formula Ia. The generic scope of Formula Ia is not coextensive with that of Formula I, and therefore there is no restriction group in which Formula Ia falls completely. Lastly, there are specific compounds which fall within the scope of Formula Ia but not Formula I. Examples of these claimed Formula Ia compounds include (but are not limited to) entries 80, 81, 441, 442, and 448 in Table A. Since the restriction groups are limited to compounds of Formula I, those compounds are not encompassed by any restriction group. The Applicants respectfully suggest that each restriction group be redrafted to encompass a Compound of Formula I and Ia and that a restriction group be added which encompasses compounds not encompassed by either Formula I or Ia.

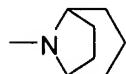
The Applicants thank the Examiner for reconsidering the plurality of the restriction groups and for rejoining Groups VI, VII, VIII, IX, and X into one group. They respectfully ask that the Office reconsider the plurality of the other restriction groups and request that Groups I, II, III, IV, and V be rejoined into one group and that Groups XI, XII, XIII, XIV, and XV be rejoined into another group.

Request for Clarification

In an Office Action dated March 31, 2008 (hereinafter “Office Action”), the Patent Office recognized nine ring systems as enabled (pages 4-5). The Applicants respectfully point out that the name in group 9), “5-methyl-2-azabicyclo[2.2.2]octane group,” is represented by the following structure:



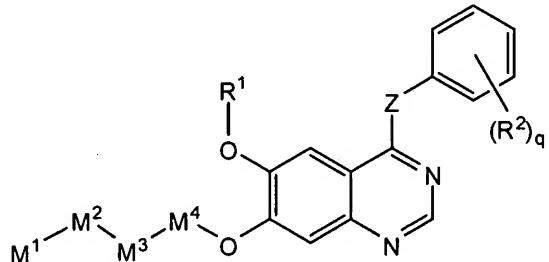
The Applicants believe the Office intended to name the group as “8-methyl-8-azabicyclo[3.2.1]octane group” which is depicted below



and is exemplified in entries 55, 57, 58, and 60 of Table A. The Applicants respectfully request clarification of which ring system the Patent Office means to describe in group 9).

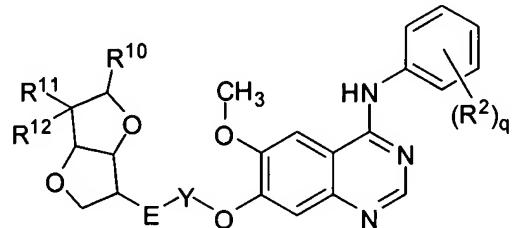
Miscellaneous

The Applicants note that the Office defined R^1 as methoxy on page four of the Office Action. However, in a Compound of Formula I,



Formula I

the oxygen is not part of Applicants’ R^1 . As the Applicants have defined it, R^1 is “C₁-C₃ alkyl optionally substituted with between one and three R^{50} substituents.” The Applicants also note that there is no R^1 group in a Compound of Formula Ia.



Formula Ia

The Applicants believe that the Office meant that a Compound of Formula I is enabled

when R¹ is methyl, and not methoxy.

In addition, on page seven of the Office Action, the Applicants respectfully point out that “R,” as referred to by the Office, is not a group that is used by the Applicants in their Compound of Formula I or Ia. They presume the Office meant to refer to R².

Objections to Claims as Containing Non-elected Subject Matter

The Claims were objected to for containing nonelected subject matter (Office Action, page four). In light of the above amendments, the Applicants believe that the basis for this objection is no longer present and respectfully request withdrawal of the objection.

Claim Objections – 37 C.F.R. § 1.75

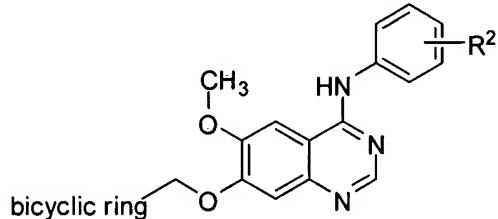
On page four of the Office Action, Claims 145 and 148 are objected to as being substantially duplicative of each other. The Applicants respectfully point out that Claim 145 is directed to a pharmaceutical composition of Claim 144 and Claim 144 covers a genus of three compounds (each optionally as a pharmaceutically acceptable salt thereof). Claim 148 is directed to a pharmaceutical composition of a single compound (optionally as a pharmaceutically acceptable salt thereof), as described in Claim 147. The Applicants respectfully submit that the scope of these two claims is substantially different and therefore request reconsideration and withdrawal of this objection.

Claim Rejections – 35 USC § 112, 1st Paragraph

Claims 67-104, 113-120, 123-125, and 137-154 are rejected as not enabled for geometric isomers or hydrates thereof (Office Action, page 5). In order to expedite prosecution, the Applicants have amended the Claims to delete “hydrate.” The Applicants respectfully point out that the term “geometric isomer” is recognized by a person of ordinary skill in the art as a subset of the term “stereoisomer” which term the Office regards as enabled. However, to expedite examination, the Applicants have deleted “geometric isomer” from the claims, making note that a geometric isomer is encompassed by the claimed term “stereoisomer.” The Applicants believe that the basis for this rejection has been removed and respectfully request that the rejection be

withdrawn.

Claims 67-104, 113-120, 123-125, and 137-154 are rejected as not enabled for compounds other than those depicted below, for convenience sake, in formula A



formula A

where R² is “a halogen, alkyl, haloalkyl, methoxy, aryloxy, or piperazinyl group” (page 4 of the Office Action) and where the bicyclic ring is selected from “1) 5-octahydrocyclopenta[c]pyrrole group; 2) 3-hexahydro-1H-[1,4]oxazino[3,4-c][1,4]oxazine group; 3) 3-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazine group; 4) 3-hexahydrofuro-[3,2-b]furan group; 5) 3-octahydro-1H-pyrido-[1,2-a]pyrazin-1-one group; 6) 3-hexahydropyrrolo[1,2-a]pyrazin-1(2H)-one group; 7) 3-hexahydrothiazolo[4,3-c][1,4]oxazine group; 8) 3-octahydro-1H-quinolizine group; and 9) 5-methyl-2-azabicyclo[2.2.2]octane group” (each as named by the Office on page 4-5 of the Office Action). Applicants respectfully request reconsideration of this rejection for the following reasons.

In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. (M.P.E.P. § 2164.04). To make a *prima facie* case of non-enablement, he or she must prove that the applicants have not shown how to make and use the invention without undue experimentation in a manner commensurate with the scope of the claims (MPEP § 2164.01). The examiner must make specific findings of fact, supported by evidence, which would allow a conclusion of non-enablement (M.P.E.P. § 2164.04). Conclusory statements, unsupported by a factual basis, are not sufficient to meet this burden.

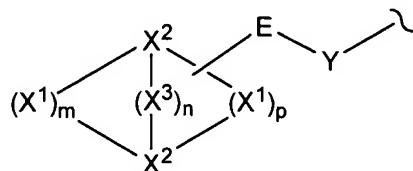
In this case, the Examiner has not met his initial burden. No findings of fact of what a person of ordinary skill in the art would know were stated in the Office Action. Specifically, the Patent Office must identify “what information is missing and why one skilled in the art could not supply the information without undue experimentation”

(M.P.E.P. § 2164.04). Here, the Office has stated that enabling disclosure is missing for everything except the scope encompassed by the working examples. Specifically, on page seven, the Office states that Applicants have “... provided no working examples of any compounds where the R, Z, and $M^1M^2M^3M^4$ moieties are not that previously defined above [in formula A, depicted above] ...” and that Applicants’ disclosure is “... not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed ...” (page seven of the Office Action). The Patent Office reaches these conclusions without considering or discussing what a person of ordinary skill in the art would know and does not offer any *specific* evidence for why the information the Office perceives as missing could not be supplied. Accordingly, the Applicants respectfully submit that the Office has not made a *prima facie* case of non-enablement.

Even if the Office had made a *prima facie* case of non-enablement, the Applicants have clearly shown how to make and use the invention enabling one of skill in the art to practice the invention without undue experimentation. The Application gives detailed procedures of how to make and use the entire claimed scope. The Applicants direct the Office’s attention to the section entitled “Synthesis of Compounds” of the Specification (pages 93-94 of the Specification). In that section, the Applicants disclose a generic scheme and description by which Compounds of the Invention can be prepared. Methods to prepare particular intermediates are described in detail in the working examples on pages 95-147 of the Specification. Further, the Applicants have provided 24 representative examples describing the synthesis and characterization of 90 compounds which are fully representative of the scope of the amended claims. In addition, the Applicants have shown how to use the full scope of the claimed invention by providing assays by which a compound can be tested to determine its activity (pages 166-170 of the Specification). The Applicants obligation is only to *show how* to use and they have done this by providing the methods to test the compounds; however, they have gone further by including biological information for over 90 compounds which are encompassed by the amended claims. (See Tables 3 and 6 of the Specification). The working examples provided in the present specification provide one of ordinary skill in the art ample

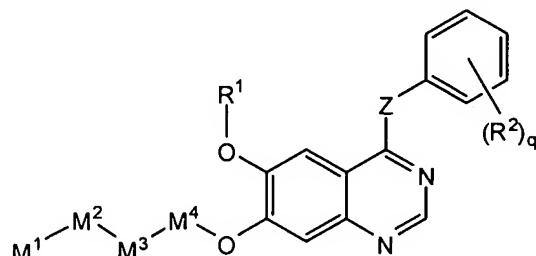
enabling support for how to make and use the entire genus of compounds claimed.

Applicants' enabling disclosure is commensurate with the scope of the claims. In particular, the Applicants have shown how to make and use the full scope of the saturated bridged ring system of Formula II



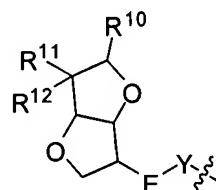
II

which makes up M¹-M²-M³-M⁴- in a Compound of Formula I:

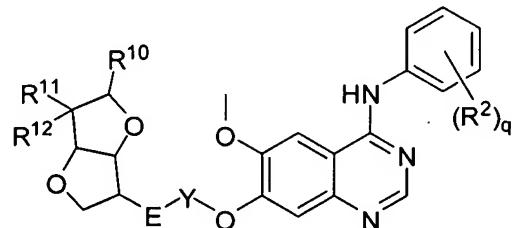


Formula I.

In addition, the Applicants have shown how to make and use the full scope of the



group which is used to make a Compound of Formula Ia:



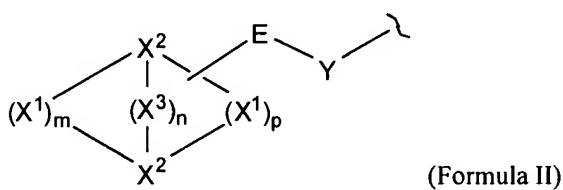
Formula Ia

Variously-sized saturated bridged ring systems are disclosed in the Specification which contain varying numbers and types of atoms at various positions in the ring and which ring systems bear various optional substituents. In particular, the Applicants claim X¹ as

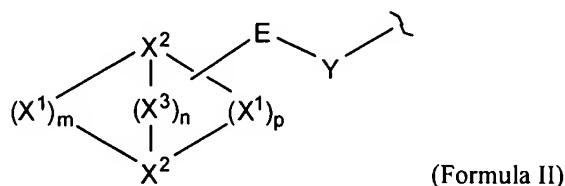
selected from $-C(R^6)R^7-$, $-O-$, $-S(O)_{0-2}-$, and $-NR^8-$; and the Applicants prepared compounds where X^1 is $-C(R^6)R^7-$, $-O-$, $-S-$, and $-NR^8-$. (See Table A, herein, for examples.) The Applicants have claimed m to be 1, 2, 3, or 4 and made compounds where m is 2, 3, or 4 (Table A). The Applicants claimed p as 1, 2, 3, or 4 and made compounds where p is 3 or 4 (Table A). The Applicants claimed n to be 0, 1, or 2 and made compounds where n is 0 or 1 (Table A). The Applicants claimed X^2 as “a bridgehead methine optionally substituted with R^6 , or a bridgehead nitrogen”, and Applicants made compounds where X^2 is either carbon or nitrogen (Table A). The Applicants claimed X^3 , when X^3 is present, as selected from $-C(R^6)R^7-$, $-O-$, $-S(O)_{0-2}-$, and $-NR^8-$ and made compounds where X^3 is not present (n is 0 indicating a bond between the two X^2 's) or is nitrogen (Table A).

Table A.

Intermediates Useful in the Synthesis of		
Example	Structure of Intermediate	Source
where m is 1		The alcohol, bicyclo[3.1.0]hexan-2-ylmethanol can be prepared according to <i>Chemische Berichte</i> (1967), 100(11), 3564-77.
where m is 2		Example 21 on page 132-3 of the Specification
where m is 3		Example 12 on page 115-6 of the Specification
where m is 4		Example 10 on page 111-112 of the Specification
where p is 1		EP413455

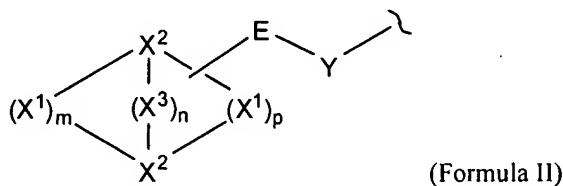


Intermediates Useful in the Synthesis of



Example	Structure of Intermediate	Source
where p is 2		The alcohol, 4-(hydroxymethyl)-1-azabicyclo[2.2.2]octane, is commercially available from SinoChemexper or can be prepared according to <i>Helvetica Chimica Acta</i> (1954), 37, 1681-8.
where p is 3		Example 25 on page 137-9 of the Specification (the di-mesylate is made from commercially available 1,4:3,6-dianhydro-D-mannitol)
where p is 4		Example 7, page 106-7 of the Specification
where n is 0		Example 13 on page 117-9 of the Specification
where n is 1		Example 20 on page 131-2 of the Specification
where n is 2		The alcohol, bicyclo[2.2.2]oct-1-ylmethanol, can be prepared according to <i>Synthesis</i> (1977), (10), 675-6.
where three X ¹ on the left side (as drawn) of the bicyclic are -C(R ⁶)R ⁷ -		Example 7, page 106-7 of the Specification
where two X ¹ on the left and right sides (as drawn) of the bicyclic are -O-		Example 19 on page 127-9 of the Specification

Intermediates Useful in the Synthesis of

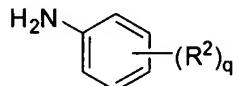


Example	Structure of Intermediate	Source
where one X^1 on the left side (as drawn) of the bicyclic is $-S-$		Example 23 on page 134-5 of the Specification
where one X^1 on the right side (as drawn) of the bicyclic is $-NR^8-$		Example 11 on page 112-4 of the Specification
where one X^2 is a bridgehead nitrogen and the other is a methine		Example 10 on page 111-112 of the Specification
where both X^2 are a methine		Example 13 on page 117-9 of the Specification
where X^3 is $-C(R^6)R^7-$		The alcohol, bicyclo[2.2.1]heptan-2-ol, is commercially available from Aldrich.
where X^3 is $-O-$		The alcohol, 8-oxabicyclo[3.2.1]octan-3-ol, can be prepared using procedures in JACS 1972, 94(23), 8124
where X^3 is $-S-$		The alcohol, (7,7-dioxido-7-thiabicyclo[2.2.1]hept-1-yl)methanol, may be prepared from 7-thiabicyclo[2.2.1]heptane-1-carboxylic acid 7,7-dioxide whose synthesis is described in J. of Org. Chem. (1969), 34(5), 1233-40.
where X^3 is $-NR^8-$		Example 20 on page 131-2 of the Specification

In addition to the disclosure in the Application, what a person of skill in the art would know must be taken into account when considering the question of enablement.

Where the Applicants have not disclosed a specific compound with a bicyclic ring of a particular size and structure, one of ordinary skill in the art would know how to make that compound using known methods and commercially available reagents. See Table A, herein, for examples. The bicyclic groups in Table A represent a few examples of what is known in the art. The Applicants note that a patent need not teach, and preferably omits, what is well known in the art (M.P.E.P. § 2164.01). Applicants' disclosure for the saturated bridged ring system described by $M^1-M^2-M^3-M^4-$ is representative of the entire claimed scope and is fully enabling when combined with what a person of ordinary skill in the art would know. They respectfully request reconsideration of this rejection.

In addition to being enabling for the full scope of the saturated bridged ring system represented by Formula II, the Applicants' disclosure is enabling for the full claimed scope of q and R^2 for a Compound of Formula I and Ia. The Office only recognized the following R^2 groups as enabled: “a halogen, alkyl, haloalkyl, methoxy, aryloxy, or piperazinyl group” (page four of the Office Action, emphasis added). The Applicants note that the Office did not discuss what is enabled for the variable “ q .” By stating that R^2 can be “a” group, it appears the Office has concluded the scope is enabled only where q is one which then limits R^2 to a single group. The Applicants have extensively described how to make and use compounds where q is two or more. With respect to R^2 , they have described the synthesis of over 466 compounds which bear various, representative groups. In addition to the Applicants' working examples, aniline intermediates



substituted with the full scope of Applicants' R^2 groups are widely-available from commercial sources such as Aldrich or can be prepared using well-documented methods in the literature. The Applicants submit that the entire scope of q and R^2 , as the Applicants have defined them, are fully enabled and respectfully request reconsideration of this rejection.

Finally, the scope of Z and R^1 as claimed by the Applicants for a Compound of Formula I and Ia are enabled when the disclosure is considered in light of what a person

of ordinary skill in the art knows. On page four of the Office Action, the Patent Office recognizes enablement only where Z is -NH- and R¹ is methyl. The Applicants submit that the entire scope of Z (-OCH₂-, -O-, -S(O)₀₋₂-, -N(R⁵)CH₂-, and -NR⁵-) and R¹ (C₁-C₃ alkyl optionally substituted with between one and three R⁵⁰ substituents) is fully enabled. The Applicants direct the Office's attention to Scheme 1 of the Application which describes the synthesis of quinazoline intermediates where Z is -OCH₂-, -O-, -S(O)₀₋₂-, -N(R⁵)CH₂-, or -NR⁵- (intermediate 6, Scheme 1). Further, the synthesis of quinazoline intermediates where Z and R¹ are as the Applicants have defined them is well-known in the art. The Applicants submit that the entire scope of Z and R¹ is fully enabled and respectfully request reconsideration of this rejection.

As discussed above, the Applicants have given ample, representative examples of how to make and use the invention without undue experimentation, but the Patent Office seems to be requiring enablement for every species in the scope. The Office has stated that the Applicants have "provided no guidance, examples, or provided any chemical or biological data and/or testing results of a compound ... other than those described above with the specific residue groups and bicyclic groups mentioned" (page 5, Office Action). Applicants respectfully submit that there is no requirement that all the compounds claimed by the genus be prepared and tested for the specification to be enabling. (See *In re Angstad*, 190 USPQ 214, 218 (CCPA 1976).) In fact, courts have held that "nothing of consequence is gained by including repetitive examples in specification..." (*In re Surrey*, 151 USPQ 724, 730 (CCPA 1966)). In light of the disclosure and what a person of ordinary skill in the art would know, the Applicants submit that they have met the requirement to enable the scope as claimed.

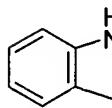
In summary, the Applicants respectfully submit that Patent Office has not met its burden to show a *prima facie* case of non-enablement as it has not provided specific findings of why a person of ordinary skill in the art could not practice the invention without undue experimentation. Even if the Office had met its burden, the Applicants have disclosed the synthesis and use of a broad range of representative compounds and are not required to list what is well known in the art, even in unpredictable arts. Given the generic disclosure in the Specification, the numerous working examples, and what is

known by one of ordinary skill in the art, Applicants submit that they have enabled the entire scope of the amended Claims. The Applicants therefore, respectfully request reconsideration and withdrawal of this rejection.

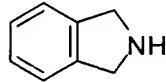
Claim Rejections – 35 USC § 112, 2nd Paragraph

The Office states that Claims 1, 2, and 4-6 are rejected as being indefinite. The Applicants previously canceled Claims 1, 2, and 4-6 in a Preliminary Amendment dated June 27, 2007. The Applicants respectfully request reconsideration as that subject matter is not being claimed in the present application.

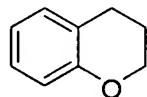
On page 9 of the Office Action, the Examiner requested clarification of which term – “aryl,” “heteroaryl,” or “heterocyclalkyl[sic]”¹ – encompasses “benzo rings fused to heterocyclic rings.” The Applicants respectfully direct the Office’s attention to the examples in the definition of “heterocyclyl” as described on page 74-75 of the Specification. Included in these examples are groups like



(indoline),



(isoindoline), and



(benzopyran). Each of

these rings includes a “benzo ring fused to a heterocyclic ring.” In addition to the examples in the definition, the “heterocyclyl” definition states that the ring can be a partially saturated bicyclic ring. A partially saturated bicyclic ring is a ring which comprises a saturated portion and an unsaturated portion. In the case of “benzo ring fused to a heterocyclic ring,” the unsaturated portion is aromatic. Accordingly, the Applicants submit that “benzo rings fused to a heterocyclic rings” fall within the definition of “heterocyclyl.”

Claims 1, 2, and 4-6 are rejected as being indefinite for failing to describe what substituents are included in the term “substituted.” The Applicants respectfully point out that these claims are no longer in the Application. With respect to pending claims, the

¹ The Applicants respectfully point out that “heterocyclalkyl” is not a term used in the Application. The term “heterocyclalkyl” is in the Application (page 74-75 of the Specification) but is defined, in part, as “a residue in which a heterocyclyl is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical.” The Applicants believe that the Examiner meant to refer to the term “heterocyclyl” or “heteroalicyclic” and not “heterocyclalkyl[sic].”

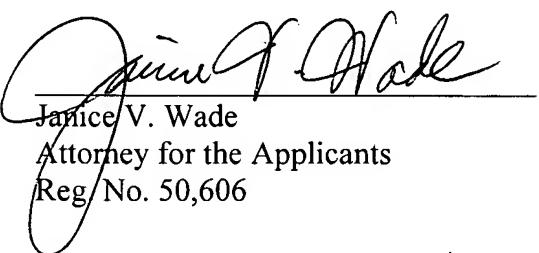
Applicants direct the Office's attention to the Preliminary Amendment filed on December 19, 2007 in which amendment the Applicants either incorporated into the claims various substituents from the term "substituted," as defined in paragraph [0116] on page 76 of the Specification, or the Applicants deleted the possibility of a substituent, e.g. "optionally substituted lower alkyl" became "lower alkyl" for certain R groups. Therefore, the Applicants respectfully request that this rejection be withdrawn.

SUMMARY

In view of the foregoing, the Applicants believe the Application is in condition for allowance and respectfully request entry of the amendments and reconsideration of the objections and rejections for the above given reasons. It is not believed that a fee is due with the submission of this response. Should any fees be required by the USPTO in order to process this submission and the papers attached, the Commissioner is hereby authorized to charge the necessary fees to Deposit Account Number 50-1108.

Respectfully submitted,

June 27, 2008
Date


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